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# Coarse-grained interactions between lipid bilayers

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## Introduction

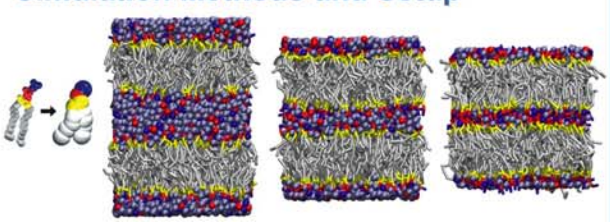
Membrane fusion is an important event underlying many cellular processes, such as viral infection, vesicle fusion and exocytosis. While some of the general principles underlying fusion are known, the specific molecular level interactions between bilayers prior to the process of fusion have yet to be discovered.

During the course of normal cell functioning, lipid bilayers must maintain impermeability and structural integrity. However, the process of fusion necessitates a transient destabilization of this integrity while the two leaflets of the bilayer rearrange to incorporate the new membrane. In the cell, this process is highly regulated by proteins; however, it has been shown that under the right conditions lipid vesicles can spontaneously fuse. We would like to parse the balance of van der Waals and electrostatic interactions leading to the critical destabilization events prior to transient disruption of bilayer structural integrity necessary for fusion events.

We have used a coarse-grain lipid model (Marrink et al, J. Phys Chem B. (2004) 108, 750) to study bilayer-bilayer interactions. Coarse-grain models of bilayers go back to the pioneering studies of lipid self-aggregation by Lipowski and colleagues. They have also been successfully used to address problems at time and length scales inaccessible to conventional all atom approaches, such as phase transitions, hydrophobic matching and domain formation.

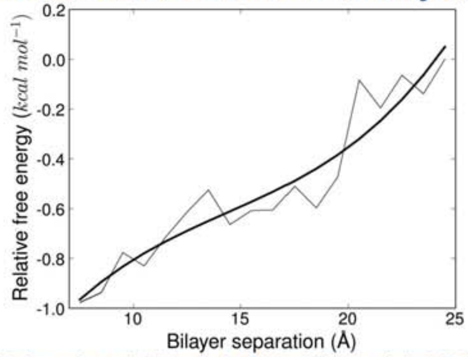
Specifically we have computed a potential of mean force (PMF) as a function of bilayer separation using the methodology of weighted histogram analysis (WHAM). We are also performing this computation with the CHARMM all-atom model (see adjacent poster). A comparison of these PMFs should shed light on the molecular determinants underlying the transient instabilities that occur as two bilayers are brought together.

## Simulation Methods and Setup



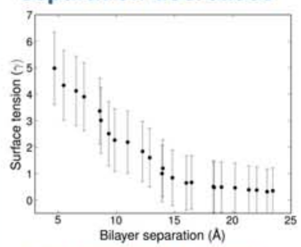
- Double bilayer system per central unit cell
- 256 DPPC lipids per bilayer (512 lipids total)
- Bilayer to bilayer distance constrained with a harmonic potential (spring constant of 2 kcal mol$^{-1}$ Å$^{-2}$))
- Constant surface area of 64 Å$^2$/ lipid (equilibrium area for DPPC)
- Simulated using the NVT ensemble so as not to impose pressure restraints in the z direction (thus complicating PMF calculation)
- Coarse-grain model of Marrink uses cutoff electrostatics (12 Å)
- Over 200 windows for PMF calculation, ~200 ns/window
- Several unbiased calculations along the reaction coordinate also performed for 400 ns

## Potential of mean force (PMF) shows a slight qualitative attraction between both bilayers



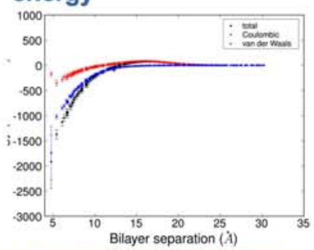

Potential of mean force calculated using the Weighted Histogram Analysis Method, which combines data from over 200 windows to generate the PMF.

## Surface tension increases as bilayer separation decreases



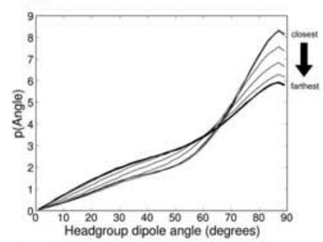

Surface tension normal to the double bilayer calculated from the set of unbiased simulations

## Breakdown of bilayer-bilayer interaction energy



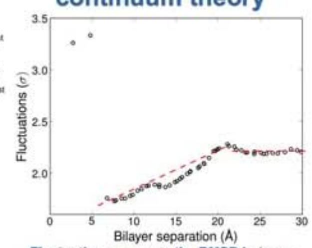

Enthalpic interaction energy computed with a cutoff of 80 Angstroms

## Headgroups flatten out for bilayers at close approach



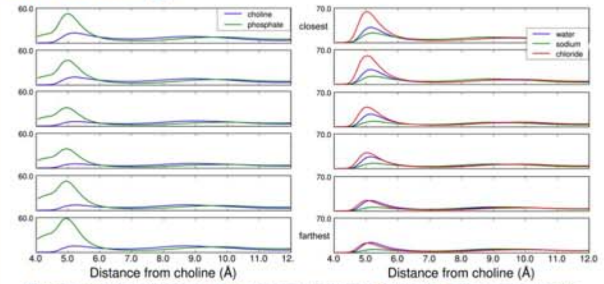

Headgroup dipoles are calculated with respect the the normal of the bilayer.

## Bilayer fluctuations tie back into continuum theory



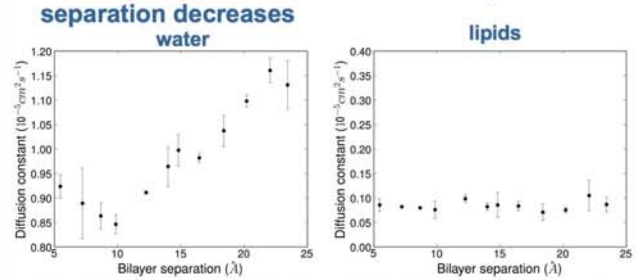

Fluctuations measure the RMSD between the average bilayer position and internal lipid displacements normal to the bilayer.

## Structural distributions around headgroup atoms do not change



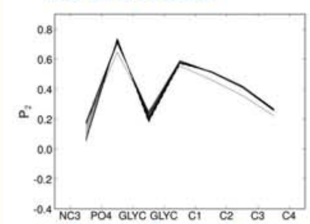

Radial distribution functions of the headgroup atoms(left) and the environment (right) calculated with respect to the choline group. The pattern is similar for the phosphate group. Each RDF is normalized to bulk (at approximately 12.0 Angstroms)

## Water mobility is restricted as the bilayer separation decreases



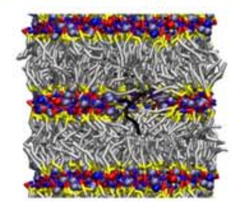

Lateral diffusion constants (parallel to bilayer surface) calculated using Einstein's relation.

## Lipid chain properties are unaffected




Order parameters are computed between subsequent bonds along the lipid molecule. Chain parameters are averaged across both alkyl groups (C1-C4).

## Evidence of lipid splay at the closest separation



Lipid splay is seen only at the closest separation

## Summary

- Both the coarse-grain and all atom results (see adjacent poster) show good qualitative agreement
- Relative free energies from the PMF show a slight attraction between the bilayers at the close separations that we have simulated
- Bilayer fluctutations are in the same range as experimental measurements on DPPC multilayers
- The predominant structural perturbations appear in the headgroup region of the bilayer